IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

LI et al.

Serial No. 09/145,180

Filed: September 1, 1998

Title: OXO-SUBSTITUTED COMPOUNDS, PROCESS...

Atty Dkt. 2824-9
C# M#

TC/A.U. 1617

Examiner: Wang, S.

Date: March 10, 2004

1617

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **0** minus highest number previously paid for **20** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **0** minus highest number previously paid for **3** (at least 3) = 0 x $ 86.00	$	0.00
If proper multiple dependent claims now added for first time, add $290.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $420.00/2 months; $950.00/3 months)	$	950.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($770.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**950.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☒ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	475.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00)	$	0.00
Other:		**0.00**
TOTAL FEE ENCLOSED	$	**475.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

1100 North Glebe Road, 8th Floor
Arlington, Virginia 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100
BJS:

NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: B Sadoff

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

LI et al. Atty. Ref.: 2824-9; Confirmation No. 5665

Appl. No. 09/145,180 TC/A.U. 1617

Filed: September 1, 1998 Examiner: Wang, S.

For: OXO-SUBSTITUTED COMPOUNDS, PROCESS...

* * * * * * * * * * *

March 10, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE

Responsive to the Office Action dated September 10, 2003, entry and consideration of the following remarks are requested.

An interview with the Examiner and the Examiner's Supervisor are requested prior to the issuance of a further Action in the event the present Response is not believed to place the application in condition for allowance. The Examiner is requested to contact the undersigned to arrange such an interview at a time convenient to the Examiners schedules.

The Examiner has withdrawn the finality of the Office Action of mailed May 24, 2002, to essentially make the same obviousness rejection without relying on one of the previously-cited references (i.e., Suto (Anti-Cancer Drug Design No. 7, pp. 107-117, (1991)). Moreover, the new Section 103 rejection no longer includes claim 196.

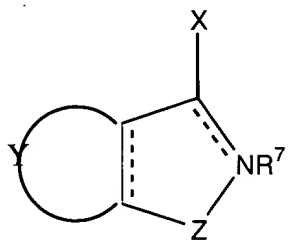
Claims 184-233 are pending and a copy of the same are attached as Appendix A to the previously-filed Appeal Brief.

Claims 193-195, 197-206, 208, 214, 215 and 217-233 have been withdrawn from consideration as being drawn to a non-elected invention. Basis for withdrawing claims 193-195 197-206, 208, 214, 215 and 217-233 from examination is not clear as all the pending claims are directed to the originally elected "method of using compounds" (Group II), as opposed to "compounds and pharmaceutical composition" (original Group I of Paper No. 10) or "method of making compounds" (original Group III of Paper No. 10). The Examiner has allowed the elected species (i.e., 5(*H*)2-nitro-10-aminophenanthridin-6-one, see, below and claim 196) and not provided a basis for withdrawing claims 193-195, 197-206, 208, 214, 215, and 217-233 from consideration, or further defined a subgenus which is the subject of the examination. See, page 1 of the Office Action dated October 30, 2000 (Paper No. 16) which only indicates that claims 193-195, 197-206, 208, 214, 215, 218, 219, 221-223, 226 and 231-233 are withdrawn from consideration. In the final rejection of May 24, 2002 (Paper No. 26), claims 193-195, 197-206, 208, 214, 215 and 217-233 have been withdrawn from consideration, again without justification or basis or explanation. The Examiner was requested in the Appeal Brief to define, with particularity, the alleged separately patentable subject matter and the scope of the present search, for clarity of the record and convenience of the Board. The Examiner is again requested to provide such a definition, for clarity of the record. This is particularly relevant as the Examiner has stated that "Search has been expanded to non-elected compound." See, page 2 of the

Office Action dated September 10, 2003 (Paper No. 32). The scope of the search however has not been defined.

Claim 196 has been objected to as being dependent upon a rejected base claim, "but would be allowable if rewritten in independent form including all the limitations of the base claim [i.e., independent claim 184] and any intervening claims." See, page 2 of the Office Action dated May 24, 2002 (Paper No. 26) and page 2 of Paper No. 32.

The claimed invention is directed to a method of inhibiting PARP activity comprising administering a compound of formula I containing at least one ring nitrogen:



and having an IC_{50} of 100 μM or lower for inhibiting poly(ADP-ribose) polymerase *in vitro*, or a pharmaceutically acceptable base or acid addition salt, prodrug, metabolite, optical isomer or stereoisomer thereof, where X is double-bonded oxygen or -OH; R^7, when present, is hydrogen;

Y represents the atoms necessary to form a fused phenyl, pyridine, or pyrimidine ring; and

Z is $-R^6C=CR^3-$ wherein R^6 and R^3, taken together, form a fused phenyl, pyridine, or pyrimidine ring; where said fused phenyl, pyridine, or pyrimidine ring of Y or Z is independently unsubstituted or substituted with at least one non-hydrogen, non-interfering substituent; and

when the Y and Z rings are phenyl and X is double bonded oxygen, at least one of the Y and Z rings contains at least one said substituent. See, page 24, line 25 - page 27, line 2, page 57, line 25 - page 67, line 5, and independent claim 184.

In another embodiment of the invention, X is double- bonded oxygen. See, page 24, line 27 and dependent claim 185.

In another embodiment of the invention, Y has at least one site of unsaturation. See, page 25, lines 20-21 and dependent claim 186.

In another embodiment of the invention, Y represents the atoms necessary to form a fused benzene or naphthalene ring. See, page 25, lines 11-14 and dependent claim 187.

In another embodiment of the invention, Y is substituted with at least one non-hydrogen, non-interfering substituent. See, page 25, lines 20-24 and dependent claim 188.

Support for the recitations of dependent claims 189 and 216 may be found, for example, at page 25, line 25 to page 26, line 29 of the specification.

Support for the recitations of dependent claim 190 may be found, for example, on page 27, line 19 to page 28, line 35 of the specification.

Support for the recitation of dependent claims 191 and 192 may be found, for example, at page 23, lines 29-37 of the specification, and originally-filed claims 48 and 49.

Support for the recitations of dependent claim 207 may be found, for example, page 54, line 9 to page 56, line 14 of the specification, and originally-filed claim 73.

Support for the recitations of dependent claim 209 may be found, for example, in originally-filed claim 77, and the corresponding portion of the disclosure.

Support for the recitations of dependent claim 210 may be found, for example, on page 57, lines 25-39, as well as the indicated support for claim 84.

Support for the recitations of dependent claim 211 may be found, for example, at page 21, line 1 of the specification.

In another embodiment of the invention, the neuronal activity of the claims includes stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration, and treatment of a neurological disorder. See, page 57, lines 29 to 32, and dependent claim 212.

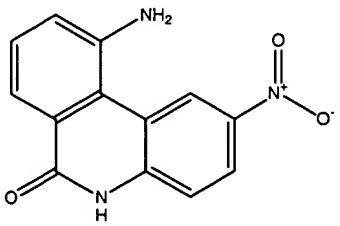
Support for the recitations of dependent claim 213 may be found at page 57, lines 35-39 of the specification.

The Section 103 rejection of claims 184-192, 207, 209-213 and 216 over Weltin et al. (Oncology Research, Vol. 6, No. 9, pp. 399-403 (1994)) in view of Banasik et al. (Journal of Biological Chemistry, Vol. 267, No. 3, pp.1569-1575 (1992)), and Endres et al. (Journal of Cerebral Blood Flow and Metabolism, No. 17, pp. 1143-1151, (1997)) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The rejection of claims 184-192, 207, 209-213 and 216 under 35 U.S.C. § 103 over Weltin et al. (Oncology Research, Vol. 6, No. 9, pp. 399-403 (1994)) in view of Banasik et al. (Journal of Biological Chemistry, Vol. 267, No. 3, pp.1569-1575 (1992)), and Endres et al. (Journal of Cerebral Blood Flow and Metabolism, No. 17, pp. 1143-1151, (1997)) should be withdrawn.

The applicants note that a species election was made in the Response of March 15, 2000, to the compound of claim 125 (now recited in pending claim 196, which has been indicated as being allowed), with a mode of delivery of sterile solution, preferably for intravenous administration, and an indication of treating ischemia/reperfusion. The Examiner has withdrawn claims 193-195, 197-206, 208, 214, 215, 218-291, 221-223, 226 and 231-233 from consideration as allegedly being drawn to a non-elected species where there is allegedly no allowable generic or linking claim. As noted above, the Examiner is not believed to have clearly defined the scope of the examination or defined the allegedly separately patentable invention. For at least clarity of the record and the convenience of the Board in any future appeal, the Examiner is requested to define the scope of the examination.

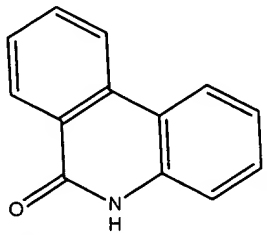
The Applicants note that the elected (and allowed) species has the following structure:



5(H)2-nitro-10-aminophenanthridin-6-one.

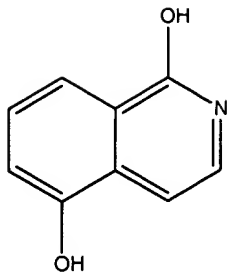
The Section 103 rejection should be reversed as the combination of cited art fails to establish a *prima facie* case of obviousness. Consideration of the following in this regard is requested.

To establish a *prima facie* case of obviousness, the cited art, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the ordinarily skilled artisan to modify a reference or to combine references, to make the claimed invention. See, *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596 (Fed.Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986) (copies previously submitted as attachments (Appendix C) to the Appeal Brief filed May 27, 2003).

The Examiner is understood to be asserting that the primary reference, Weltin, teaches that 6(5)-phenanthridinone (i.e., 

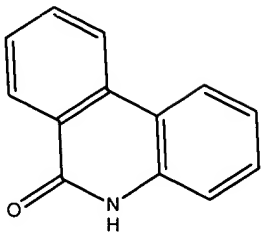
6(5H)-phenanthridinone
), is a potent inhibitor of PARP, and that one of the secondary reference, Endres, teaches a method of treating ischemia by inhibition of PARP activity. The Examiner asserts that one of ordinary skill in the art would have reasonably expected to optimize PARP inhibiting activity of 6(5H) - phenanthidinone "by adding amino and/or nitro group[s] to 6(5H)-phenanthridinone", allegedly based on Banasik's teaching of a 2-nitro substituted 6(5H)- phenanthridinone. See, pages 2-3 of Paper No. 26 and page 3 of Paper No. 32.

In fact, Weltin discusses three structurally distinct compounds that are taught to provide PARP inhibiting activity, i.e., 1, 5-dihydroxyisoquinoline;



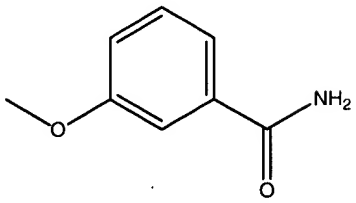
1,5-dihydroxyisoquinoline

6(5H)-phenanthridinone



6(5H)-phenanthridinone

and 3-methoxybenzamide;

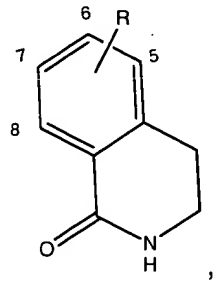


3-methoxybenzamide

Only one of these noted structures of Weltin (i.e., the 6(5H) phenanthridinone selected by the Examiner) is a phenanthridinone. Weltin, including all 3 different types of structures, must be considered as a whole. The Examiner's selection of and focus on 6(5H)-phenanthridinone is an inappropriate use of hindsight. Weltin does not provide any motivation to select the 6(5H)-phenanthridinone over the other structurally unrelated compounds.

The secondary reference, Banasik, discloses 76 different compounds, only two of which are phenanthrindinones. Absent the applicants' disclosure, there was no motivation in Banasik to focus on phenanthridinones.

The Examiner's previously cited other secondary reference, i.e., Suto, discloses that substituted isoquinolines of the following structure:

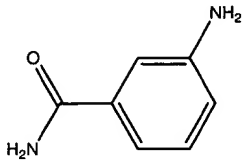


would have a wide range of activity, some of which have only minimal activity (i.e., IC_{50}= 120 uM). The Examiner has not further relied on Suto however the same forms a backdrop of the art from which one of ordinary skill had to select and the Examiner had previously indicated the same to be relevant.

It continues to be unclear from the cited art how or why one of ordinary skill would have altered one of the structures of Weltin (i.e., selecting to alter the phenanthridinone) in view of Banasik, with or without Suto. In fact, the applicants believe one of ordinary skill may have been motivated to alter, if anything, the 1,5-dihydroxyquinoline of Weltin from the teachings of substituted isoquinolines of Suto, as opposed to the 6(5H)-phenanthridinones. The fact that the Examiner has no longer relied on Suto does not negate the relevance that on of ordinary skill may have been motivated away from the presently claimed invention by art of record. By no longer

relying on Suto, the Examiner perhaps agrees that Suto teaches away from the presently claimed invention.

Finally, Endres only relates to the use of 3-aminobenzamide which has the following structure:



3-aminobenzamide

The combination, of these references would, at best, only provide an invitation to further experimentation, considering the wide range of chemical species, rather than making the presently claimed invention obvious. The Section 103 rejection should be reversed.

As a further distinction over the cited art, the appellants noted that Endres utilizes 3-aminobenzamide ("3-AB") in analyzing the function of PARP. 3-AB is fundamentally different from the compounds of the instant invention with respect to structure. 3-AB employs a free primary amine (-NH_2), as opposed to a secondary amine (-NH-) that is part of a ring structure.

Finally, the cited art fails to provide a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. See *Amgen, Inc v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991) (copy previously submitted as Appendix C attached to the Appeal Brief).

Finally, the applicants note the Examiner's unsupported conclusion that "One having ordinary skill in the art would have been motivated to prepare the instantly claimed compound [sic] because such structurally homologous are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious." See, page 3 of Paper No. 32. The Examiner is urged to appreciate however the following caution expressed by the court in In re Ochiai:

> The use of *per se* rules, while undoubtedly less laborious than a searching comparison of the claimed invention -- including all its limitations -- with the teachings of the prior art, flouts section 103 and the fundamental case law applying it. *Per se* rules that eliminate the need for fact-specific analysis of claims and prior art may be administratively convenient for PTO examiners and the Board. Indeed, they have been sanctioned by the Board as well. But reliance on *per se* rules of obviousness is legally incorrect and must cease. Any such administrative convenience is simply inconsistent with section 103, which, according to *Graham* and its progeny, entitles an applicant to issuance of an otherwise proper patent unless the PTO establishes that the invention *as claimed* in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations. We once again hold today that our precedents do not establish any *per se* rules of obviousness, just as those precedents themselves expressly declined to create such rules. Any conflicts as may be perceived to exist derive from an impermissible effort to extract *per se* rules from decisions that disavow precisely such extraction. In re Ochiai, 37 USPQ2d 1127, 1133 (CA FC 1995).

In reviewing the facts of the present application and cited art, as required according to the court in Ochiai, the applicants again submit that the presently claimed invention would not have been obvious from the teachings of the cited art.

The claims, as a whole, are submitted to be patentable over the cited art and

withdrawal of the Section 103 rejection is requested.

The applicants again request an interview with the Examiner and the Examiner's Supervisor, prior to issuance of a further Action, in he event the present Response is not believed to place the application in condition for allowance.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100